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Health and Environmental Effects Profile for Malathion

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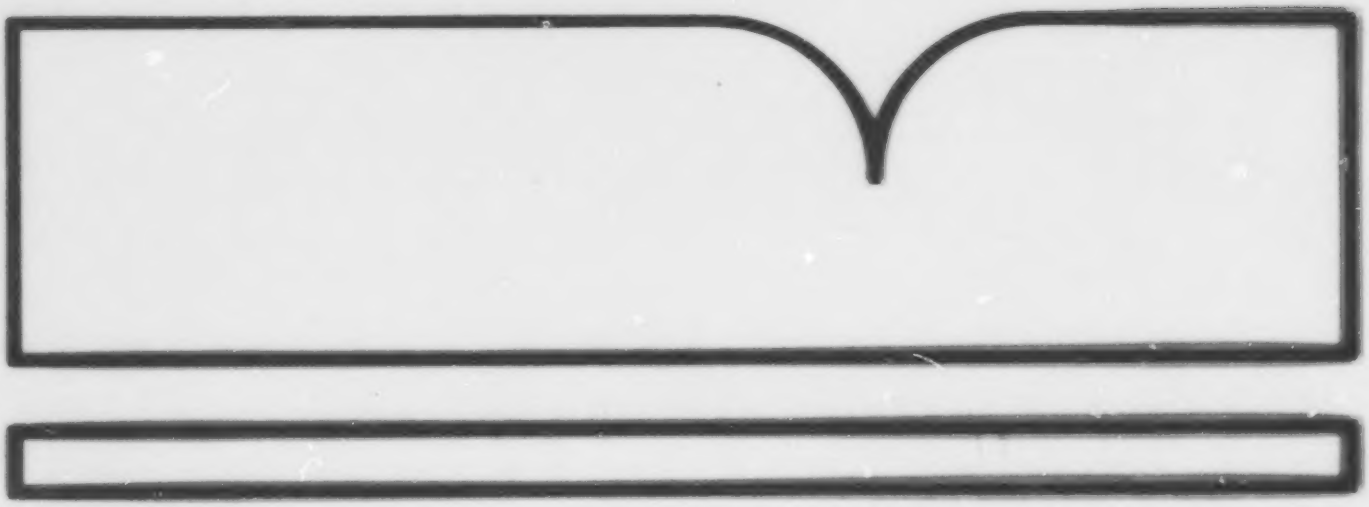

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR MALATHION

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
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16. ABSTRACT

The Health and Environmental Effects Profile for malathion was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Malathion has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for malathion is 0.02 mg/kg bw/day for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a relase as specified by CERCLA based on chronic toxicity. Existing data are insufficient to determine an RQ value.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1984.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

TABLE OF CONTENTS

		Page
1.	INTRODUCTION	1
1.1.	STRUCTURE AND CAS NUMBER	1
1.2.	PHYSICAL AND CHEMICAL PROPERTIES	1
1.3.	PRODUCTION DATA	2
1.4.	USE DATA	2
2.	ENVIRONMENTAL FATE AND TRANSPORT PROCESSES	3
3.	EXPOSURE	11
4.	PHARMACOKINETICS	13
4.1.	ABSORPTION	13
4.2.	DISTRIBUTION	14
4.3.	METABOLISM	15
4.4.	EXCRETION	18
5.	EFFECTS	21
5.1.	CARCINOGENICITY	21
5.2.	MUTAGENICITY	26
5.3.	TERATOGENICITY	30
5.4.	OTHER REPRODUCTIVE EFFECTS	30
5.5.	CHRONIC AND SUBCHRONIC TOXICITY	31
5.6.	OTHER RELEVANT INFORMATION	35
6.	AQUATIC TOXICITY	38
6.1.	ACUTE TOXICITY	38
6.2.	CHRONIC STUDIES	44
6.3.	PLANT EFFECTS	50
6.4.	RESIDUES	50
6.5.	OTHER RELEVANT INFORMATION	51
7.	EXISTING GUIDELINES AND STANDARDS	52
7.1.	HUMAN	52
7.2.	AQUATIC	52
8.	RISK ASSESSMENT	53
9.	REFERENCES	57
	APPENDIX: LITERATURE SEARCHED	84

LIST OF TABLES

No.	Title	Page
5-1	Incidences of Proliferative Lesions of the Thyroid in Malathion Treated Rats.	22
5-2	Incidence of Hepatocellular Lesions in Male B6C3F1 Mice Treated with Malathion.	25
5-3	*In Vitro* Mutagenicity of Malathion.	27
5-4	Acute Toxicity of Malathion	36
6-1	Acute Lethal Concentrations (LD_{50}s) of Malathion to Freshwater Fish	39
6-2	Acute Lethal Effects of Malathion on Aquatic Invertebrates. .	45

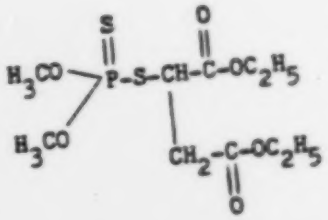
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
DNA	Deoxyribonucleic acid
EC_{50}	Median effective concentration
EEG	Electroencephalography
EMG	Electromyography
GI	Gastrointestinal
i.p.	Intraperitoneal
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Lethal dose to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
LOEL	Lowest-observed-effect level
MATC	Maximum acceptable toxicant concentration
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ppm	Parts per million
ppt	Parts per trillion
SCE	Sister-chromatid exchange
UV	Ultraviolet
WHO/FAO	World Health Organization/Food and Agriculture Organization

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Malathion is the common name for S-1,2-di(ethoxycarbonyl)ethyl O,O-dimethyl phosphorodithioate (Martin and Worthing, 1977). Other common names for this compound include the following: Butanedioic acid, [(dimethoxyphosphinothioyl)-thio]-diethyl ester (U.S. EPA/NIH, 1983); diethyl(dimethoxyphosphinothioyl)-thiobutanedioate; formerly diethyl mercapto succinate S-ester with O,O-diethyl phosphorodithioate (Martin and Worthing, 1977); calmathion; carbetox; emmatos; fosfothion; malatox; malphos; sadafos; and carbofos (NIOSH, 1983). This insecticide was introduced in 1950 by American Cyanamid Company under the code number "EI4049" and the trademark Cythion. Other trademarks include Malathion, Malathiozol and Malathiozoo (Martin and Worthing, 1977). The structure of malathion is depicted below (Martin and Worthing, 1977):



The molecular formula for malathion is $C_{10}H_{19}O_6PS_2$ and the molecular weight is 330.3. The Chemical Abstracts Service (CAS) registry number for this compound is 121-75-5.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Malathion is a clear amber liquid, which is soluble in water to 0.0145% and miscible with many organic solvents (Metcalf, 1981). Malathion is stable in natural fresh and saline water at pH 5-7. Highly acidic (pH<2) or

alkaline (pH>9) media increase hydrolysis at rates dependent on temperature and pH (Martin and Worthing, 1977). Some of the physical properties of malathion are listed below:

Melting point:	2.85°C (Martin and Worthing, 1977)
Boiling point:	156-157°C at 0.7 mm Hg (Martin and Worthing, 1977)
Vapor pressure:	4×10^{-5} mm Hg at 20°C (Verschueren, 1983)
Solubility in water:	145 mg/L at 25°C (Martin and Worthing, 1977)
Octanol/water partition coefficient:	781 (log 2.89) (Mulla et al., 1981)
Specific gravity:	1.23 (IARC, 1983)

1.3. PRODUCTION DATA

Malathion is prepared by the addition of O,O-dimethyl phosphorodithioic acid to diethyl maleate, hydroquinone being present to suppress the polymerization of the unsaturated ester (Martin and Worthing, 1977). Malathion is produced by the American Cyanamid Company in Linden, NJ (SRI, 1983). Recent production data for the United States were unavailable; however, the amount produced in 1976 was estimated at 35 million pounds, and a 10 million dollar expansion was planned for 1977 (Ayers and Johnson, 1976). In 1978, its production is estimated to have been 14 million kg (IARC, 1983).

1.4. USE DATA

Malathion is a nonsystemic insecticide and acaricide. It is used on a wide range of agricultural and horticultural crops including forage crops, fruit and vegetable crops, cotton, and forest and shade trees. It is also used to control mosquitos, flies, household insects, animal ectoparasites and human head and body lice (Martin and Worthing, 1977).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

The fate and transport of malathion in the environment has been well characterized. The persistence of malathion in aquatic systems will be influenced by physical, chemical and biological factors. This compound can undergo relatively rapid hydrolysis in saline alkaline environments at high temperatures but is more persistent at acidic and neutral pHs. Microbial degradation also can play a major role in the disappearance of this compound from the aquatic environment, especially under conditions where hydrolysis is not the major degradative pathway.

The persistence of malathion in solution as a function of pH has been reported by several researchers. The variations noted in these studies appeared to be due to specific environmental conditions. For example, Cowart et al. (1971) reported that malathion underwent 91% hydrolysis in 4 weeks at pH 6.0 in sterile buffered water. A half-life of 7.8 hours was reported by Ruzicka et al. (1967) for malathion in ethanol-buffer (20:80, pH 6.9) at 70°C. The products of hydrolysis were dimethylhydrogen phosphodithioate and diethyl fumarate. Konrad et al. (1969) measured 100% degradation in 7 days at pH 11 and 25% at pH 9 in 7 days. The degradation products formed were thiomalic acid and dimethyl thiophosphate. Freed et al. (1979a,b) found that loss of malathion was influenced by pH and temperature. At 20°C and pHs of 7.4 and 6.1, malathion had a half-life of 10.5 days and 120 days, respectively; at 37.5°C and pH 7.4, the half-life was 1.3 days. Rates of hydrolysis were also reported by Wolfe et al. (1977). Malathion was reported to be stable at pH 2.6 in aqueous solution for up to 10 days. At pH 8, half-lives were 36 hours at 27°C, 1 hour at 40°C and 40 days at 0°C. At 27°C the products formed included malathion, 50%; malathion monoacid, 15%; diethyl fumarate, ethyl hydrogen fumarate and 0,0-dimethyl

phosphorodithioic acid, 35%. A half-life of 22 hours was also measured for malathion in natural river water (pH 8.2) at an unspecified temperature (Wolfe et al., 1977). The second order rate constant for alkaline hydrolysis at 27°C was 5.5 ± 0.3 $M^{-1}S^{-1}$.

In a field study, Guerrant et al. (1970) found that 65% of the aerially applied malathion reached water or land; the maximum concentration found in water (32 sites) 4 hours after spraying was 0.51 ppm. Malathion half-lives for hydrolysis in these waters would vary from 0.5-10 days, based on the hydrolysis rate at pH values varying from 6.8-9.5. After 48 hours, however, only two sites contained detectable residues (0.001 and 0.006 ppm, down from 0.021 and 0.082 ppm, respectively).

Malathion degradation in aqueous systems was found to be influenced by salinity and temperature. Walker (1978, 1976) found that malathion degradation increased as the salinity and temperature of the seawater increased. At 30°C, the half-life of malathion was <2 days in seawater containing 1.0, 2.0 or 2.8% salt compared with 11 days in freshwater. At 20°C degradation was complete in 15 days at 2.8%, 20 days at 2.0% and 25 days at 1.0%, compared with 67% degradation in 40 days for malathion in freshwater. At 10°C the rate of degradation was further reduced to 70 days for an 89-97% loss of malathion in seawater of 2.8 to 1.0% salinity. At the same temperature, only 27% was degraded in 70 days in freshwater. Bourquin (1977) also observed an increase in degradation of malathion with increasing salinity. The half-life of malathion in 10, 20 or 30% seawater (27°C and pH 7.2) was ~12.5, 5 and 3 days, respectively. The degradation product present at 2 days was malathion monocarboxylic acid, and at 7 days, malathion dicarboxylic acid.

The effect of UV light on malathion has been reported by Cook (1955), Cook and Ottes (1959) and Mitchell (1961). Malathion was degraded under UV light (2537 Å); however, none of the products were identified. Wolfe et al. (1977, 1976) reported a half-life of 990 hours in distilled water (pH 6.0) and 15-16 hours in natural water when malathion was irradiated with wavelengths of >290 nm. Malathion was also found to be unreactive toward singlet oxygen in both distilled water and acetonitrile (Wolfe et al., 1976).

Degradation of malathion by microorganisms in aqueous systems has been well studied. Paris et al. (1981, 1975a) observed 50% degradation of malathion in 32 hours by a heterogeneous bacterial population isolated from river water. The major metabolite was identified as malathion ß-monoacid (99%); only 1% of the malathion was transformed to malathion dicarboxylic acid, O,O-dimethyl phosphorodithioic acid and diethyl maleate. From a comparison of distilled and natural river water, Eichelberger and Lichtenberg (1971) concluded that the degradation (90% in 2 weeks) of malathion in natural water was brought about by the activity of microorganisms. Rapid degradation by 11 pure cultures of bacteria isolated from a salt marsh by the enrichment technique was also observed. Degradation of malathion to 10 metabolites was reported, including malathion monoacid, dicarboxylic acid, desmethyl malathion and a number of phosphodithionates (Bourquin, 1977). Lewis et al. (1975) isolated from a freshwater pond a fungus, Aspergillus oryzae, which was capable of transforming malathion to malathion ß-monoacid (97%) and malathion dicarboxylic acid (3%); however, the rate of this conversion was slower than that observed for pure cultures of bacteria. Similar results were obtained by Paris et al. (1975b), who found that bacterial removal of malathion in vitro was ~5000 times faster than fungal removal under the same conditions. Further, rapid disappearance of malathion was

observed in a mixed culture of bacteria and fungi (half-life of 2.2 hours). The major metabolite formed in the mixed culture was malathion B-monoacid (97-99%). Also detected were malathion dicarboxylic acid in the bacterial and fungal systems and O,O-dimethyl phosphorodithioic acid and dimethyl maleate in the bacterial system.

Rapid metabolism of malathion by algae was observed by O'Kelley and Deason (1976) and Moore and Dorward (1968). At 1 ppm malathion concentration in the algal culture, Gonuim pactorale, 55.7% of the applied malathion was metabolized in 4 days (Moore and Dorward, 1968). At the same concentration, half-lives of 1.5-2.9 hours were reported for malathion in pure cultures of Chlorella sp. and 10.8-15.9 hours in Anacystis nidulans, compared with 116.4-240.2 hours for the control (no algae) (O'Kelley and Deason, 1976).

The transport of malathion in the aquatic environment will depend on the ability of the compound to adsorb to particulate organic matter, to volatilize or to bioaccumulate in aquatic organisms. Meyers et al. (1970) reported that malathion was strongly adsorbed to pond sediments with high clay and silt contents. Kenaga (1980) predicted a soil sorption coefficient of 280 for malathion from its water solubility, which suggests that the compound has a moderate potential to sorb to organic matter. Documentation of malathion loss through volatilization from water was not located; however, based on its calculated Henry's Law constant, its loss from the water through volatilization is unlikely to be on the same order as biodegradation (Lyman et al., 1983). Belluck and Felsot (1981) determined a BCF of 1 for malathion in caddisfly egg masses. Kenaga (1980) calculated a BCF of 37 for malathion from binary regression equations. Based on these data, malathion is not expected to bioaccumulate significantly in aquatic organisms.

The fate of malathion in soil will be dependent on pH, temperature, organic matter and moisture content. Walker and Stojanovic (1973) reported that malathion was susceptible to hydrolysis in the alkaline pH range. Using three sterile soils, the investigators found that loss of malathion (16 ppm) through chemical degradation during a 7-day incubation was 18% in Okolona clay, 10% in Trinity loam and 6% in Freestone sandy loam. Excluding the effect of microorganisms by sterilization, the high degradation in the Okolona clay could have been attributed to high pH (7.4) and high moisture content. In Trinity loam, the pH difference compared with the Okolona clay was very small, but the higher organic matter content (4.7%) in the Trinity loam could have caused absorption rather than degradation of the insecticide. The lowest hydrolysis in Freestone sandy loam could have been due to the low pH (5.3) and low moisture content of the soil (Walker and Stojanovic, 1973).

Konrad et al. (1969) reported that pH was probably the dominant factor in in ^{14}C-malathion degradation both sterile (irradiated) and nonsterile Poygan silty clay (pH 7.2), Kewaunee clay (pH 6.4), and Ella sandy loam (pH 3.8) soils; 97% removal was complete within 70 hours for all soils. The half-lives were 6, 8 and 25 hours for Poygan, Kewaunee and Ella soils, respectively. Konrad et al. (1969) suggested that a chemical reaction rather than microbial degradation was occurring, although hydrolysis in water (pH <9) was slow. Diethyl thiomalate was found to accumulate in the soils.

The short persistence of malathion in soils, apart from chemical and photochemical degradation, is due to microbial breakdown. In a laboratory study, when added to a culture of Bacillus subtilis, malathion residues (20 ppm) disappeared completely within 8 days (Yasuno et al., 1965). Matsumura

and Boush (1966) reported that a soil bacterium, Pseudomonas sp., and a fungus, Trichoderma viride, were found to be active in deethylation of the carboethoxy moiety in the side chain of malathion (carboxyesterase activity). Some of the variants of T. viride also showed high demethylation activities, suggesting another degradation pathway. Rosenberg and Alexander (1979) also reported degradation of malathion to dimethyl phosphorodithioic acid by 2 strains of Pseudomonas. A half-life for this transformation was ~28 hours.

Walker and Stojanovic (1973) reported that the breakdown of malathion in 3 nonsterile soils was 77-95% within 10 days at pH 5.3-7.4 and 25-26°C. Walker and Stojanovic (1974) isolated five cultures capable of 47-95% malathion degradation in 7 days. The degrading organisms in these soils were bacteria, fungi and a Streptomyces sp. A bacterium, Arthrobacter sp., degraded malathion into mono- and diacid and dimethyl phosphorthio- and dithioate derivatives. Degradation of p,p'-malathion by the bacteria, Rhizobium trifoli and R. leguminiosauim, was observed by Mostafa et al. (1972). After 1 week of incubation at 30°C and pH 6.0, 87 and 67% of the applied malathion was metabolized by the two organisms to inorganic phosphates, mono- and diacid, dimethyl phosphate, O,O-dimethyl phosphorothioate and O,O-dimethyl phosphorodithioate. From a comparison of nonsterile and sterile estuarine sediment, Walker (1976) concluded that the breakdown of malathion was brought about by four species of bacteria. In sterile samples, 57% was lost in 11 days, and in nonsterile samples 100% was lost in 3 days. Degradation also increased as the salinity increased. At 2.5% salinity, 97% of the malathion was lost in 7 days and at 0% salinity, 53% was lost within the same period.

The two processes that may influence the transport of malathion in the soil are leaching and volatilization. Both processes will depend on the degree of adsorption between the malathion molecules and the soil complex.

Jenkins et al. (1978) reported on the leaching of malathion from lysimeters and in field plots. The lysimeter studies used the following soils: Delta peat (24.5% total carbon), Oakley sand (0.02% total carbon), Reiff very fine sandy loam (0.55% total carbon), Yolo silty clay loam (0.93% total carbon) and Gravelly River sand (0.33% total carbon). The field studies used Yolo silty clay loam and Reiff very fine sandy loam. During the lysimeter studies, malathion was added at 0.1 ppm in wastewater sludge effluent at the rate of 5.1 cm/week (12.1 ℓ) for 14 weeks. Over this period, malathion was detected sporadically in the lysimeter soils. At the end of the study (39 weeks), malathion was detected at the 15 cm level of Reiff, Delta peat and Gravelly River sand at 1-5 µg/kg. Low concentrations (<1 µg/kg) of malathion were observed in the Yolo soil below 50 cm; no malathion was detected in the Oakley soil. The effluent water was also sampled for malathion; concentrations >1 µg/ℓ level occurred only rarely. Finally, air samples taken above the lysimeters revealed losses between 9.5 and 47.7 ng malathion in a 22-hour period.

In field studies, Jenkins et al. (1978) sprayed malathion at 0.1 ppm in wastewater at a rate of 5.1 cm weekly for 15 weeks. Malathion was never detected at levels >2 µg/kg in the soil and 1 µg/ℓ in the water.

MacNamara (1969) and MacNamara and Toth (1970) studied the absorption of malathion on clays, humic acids and soils. Malathion adsorption onto kaolinite and illite clays were cation dependent, while adsorption onto montmorillonite was high regardless of cation. Adsorption onto humic acids was higher than clays. Bowman (1970) reported that malathion penetration onto

Na-, Ca-, Cu-, Al- and Fe-montmorillonite clay was slow below 30% relative humidity (RH) but occurred within minutes at ≥40% RH. Sorption increased when water was removed from the clays as evidenced by lowering of the characteristic carbonyl stretching frequency. LaFleur (1979) found the adsorption of malathion to the components of two soils (1.15 and 1.90% organic matter; pH 6) to be relatively complete within 10^4 minutes. Desorption was negligible during the same time period. Meyers et al. (1970) reported that malathion was highly adsorbed to watershed soils that were high in clay and silt. Kenaga (1980) calculated a soil sorption coefficient of 280 from binary regression equations. These data suggest that malathion may be moderately sorbed to soils.

Harris and Lichtenstein (1961) found no evidence of volatilization of malathion from dry quartz sand treated at 4 ppm. Residue determinations were based on the mortality of two insects exposed for 24 hours over the treated soil; thus, this method may not have been sensitive enough.

Data regarding the leaching and movement of malathion in soil were not located in the available literature; however, based on the water solubility, soil sorption coefficient (Kenaga, 1980), adsorption studies and degradation studies, some leaching may occur in soils with low clay and organic matter, and low pH.

Data regarding the fate and transport of malathion in the atmosphere were not located. Since the vapor pressure of malathion is $>10^{-7}$ torr, adsorption to particulates and dry deposition probably will not be dominant removal mechanisms (Cupitt, 1980). Washout may occur, although no evidence of this was found in the available literature.

3. EXPOSURE

STORET contained observations for 4653 stations for malathion in water. The overall analysis included concentrations of 0-29700.0 µg/ℓ with a mean of 1.319 µg/ℓ (N=39530) for malathion in whole water samples; 0-750.0 µg/kg with a mean of 3.6 µg/kg (N=4131) for malathion in mud; 0-0.3 µg/ℓ with a mean of 0.0025 µg/ℓ (N=360) for malathion in the filtered fraction; and 0.05-0.5 µg/kg with a mean of 0.181 µg/kg for malathion in wet tissue.

Duggan et al. (1983) reported on pesticide residue levels in food between July 1, 1969 and June 30, 1976. Malathion was detected in 289 of 1980 composites, an average of 14.6% from 1971-1976. The average positive detections for the years 1971-1976 were 13.6, 16.7, 15.0, 14.7, 14.2 and 12.1%, respectively. In 1977 and 1978, malathion was detected in 15.0 and 17.1% (300 and 240) of the composites, respectively (Johnson et al., 1984; Podrebarac, 1984). The crops with the most frequent residues were ready-to-eat grain and cereal products, 97.6% positive (0.020 ppm average); domestic nuts, 61.1% positive (1.732 ppm average); peanuts, 14.8% positive (0.712 ppm average); and soybeans, 42.1% positive (0.051 ppm average) during 1970-1976 fiscal years (Duggan et al., 1983).

Numerous studies including Stevens et al. (1970), Wiersma et al. (1972), Guerrant et al. (1970), Lenon et al. (1972) and Carey et al. (1979a) and the National Soils Monitoring Program (Crockett et al., 1974; Carey et al., 1978; Carey et al., 1979b) have shown low or no residue levels of malathion in soils where it has been used. For example, Stevens et al. (1970) analyzed 17 fields with records of malathion application but only detected malathion in one field for which no record of application was found. The residue levels in this field were 0.03 ppm. Carey et al. (1979a) found

no organophosphorus pesticide residues including malathion in urban and suburban soils from five metropolitan areas. Although the data are difficult to summarize because of differences in reporting, malathion appears to have been detected in <1% (0.2-0.1%) of all the sites monitored in the National Soils Monitoring Program; it appears to have been used on >6% of the sites. In 1971 and 1972, three positive values were detected; the maximum level was 0.19 ppm dry weight.

A maximum concentration of 2.0 ng/m^3 malathion was measured in air surrounding Orlando, FL in 1971 (Stanley et al., 1971). Only 4 of 99 samples were positive; Baltimore, Buffalo, Dothan (AL), Fresno (CA), Iowa City, Riverside (CA), Salt Lake City and Stoneville (MS) air samples had malathion concentrations below the detection limits (776 total samples).

Although no data were available that described the numbers of workers exposed to malathion during agricultural activities, on the basis of the 1974 National Occupational Hazard Survey, NIOSH (1980; 1981) estimated that ~126,000 U.S. workers in 73 nonagricultural industries were exposed to malathion (IARC, 1983).

4. PHARMACOKINETICS

4.1. ABSORPTION

Ahdaya et al. (1981) and Ahdaya and Guthrie (1982) investigated the absorption of [^{14}C] malathion (succinyl labeled) following oral administration of 1 mg/kg bw to fasted female ICR mice. Based on the amount of radioactivity remaining in the GI tract, malathion was rapidly absorbed ($t_{1/2}$=33.5±2.6 minutes), with 88.8% of the administered dose being absorbed within 1 hour. When absorption was limited to the stomach, by ligation of the pylorus, only 19.7% of the administered radioactivity was absorbed within the first hour, implying that the majority of the malathion absorption occurs in the intestine.

Dermal absorption has been investigated by Shah et al. (1981), Wester et al. (1983) and Murphy (1980). Murphy (1980) demonstrated that malathion applied to the skin (>1 g/kg) of rats did not inhibit brain acetylcholinesterase, implying that absorption was not extensive. Shah et al. (1981) found that dermal absorption of malathion by ICR mice was slower ($t_{1/2}$= 129.7±47.7 minutes) than was the absorption of any of the other insecticides tested: carbaryl (12.8±4.1 minutes), methomyl (13.3±2.8 minutes), carbofuran (7.7±1.5 minutes), parathion (66.0±21.9 minutes), chlorpyrifos (20.6± 5.9 minutes), methyl chlorpyrifos (51.6±6.5 minutes), nicotine (18.2±2.4 minutes), permethrin (5.9±1.3 minutes), DDT (105.4±25.6 minutes), hexachlorobiphenyl (43.8±7.0 minutes), 4-chlorobiphenyl (16.8±2.3 minutes), chlordecane (41.3±8.8 minutes), and dieldrin (71.7±17.3 minutes). Wester et al. (1983) studied the dermal absorption of ^{14}C-malathion by five male volunteers. ^{14}C-malathion (20 µL applied to 4.6 cm² area or 5 mg/cm²) was applied to the forearms on day 1 and day 8 of the the study. On days 2-7 and 9-14 of the study, nonlabeled malathion was applied daily

at 5 mg/cm² doses. Urinary excretion of radioactivity was followed, and the percent of the dose absorbed was determined assuming that 90.2% of the absorbed ^{14}C-malathion would be excreted in the urine. No significant differences between absorption of the first dose of ^{14}C-malathion (4.48±1.3% over 7 days) and the second dose of ^{14}C-malathion (3.53±1.0% over the next 7 days) were found.

Maibach et al. (1971) studied the dermal absorption of ^{14}C-malathion (4 µg/cm²) by various regions of the body relative to the absorption by the forearm in normal male volunteers. Urinary excretion of radioactivity at intervals up to 24 hours was used as an index of absorption. The ratios comparing absorption of ^{14}C-malathion by the various sites with that of the forearm were as follows: forearm, 1.0; palm, 0.9; ball of foot, 1.0; abdomen, 1.4; hand dorsum, 1.8; forehead, 3.4; and axilla, 4.2.

4.2. DISTRIBUTION

Ahdaya et al. (1981) determined the distribution of ^{14}C in fasted female ICR mice given [succinyl-^{14}C] malathion (1 µ Ci, 1 mg/kg). Radioactivity in the blood reached peak levels (4-5% of the dose) in ~10 minutes, dropped to 2-3%, and remained at this level for the remainder of the 60-minute observation time. Radioactivity in the liver followed the same time course, with peak levels of ~6% of the administered dose.

Bourke et al. (1968) administered [succinyl-^{14}C] malathion (5 µ Ci, 25 mg) in corn oil to 6 male Holtzman rats by gavage. At 8 hours after dosing, half of the administered radioactivity remained in the GI contents (46.65±7.32%). The blood (0.78±0.17%), GI tract (0.30±0.03%), liver (0.28±0.07%) and kidney (0.09±0.03%) also contained significant amounts of ^{14}C. By 24 hours, most of the radioactivity had been absorbed and excreted (92%); however, significant amounts still remained in the GI con-

tents (7.75±2.13%), blood (0.20±0.05%), GI tract (0.05±0.01%), liver (0.18±0.03%) and kidney (0.05±0.03%). These data indicate that radioactivity is lost from the liver at a slower rate than from other organs or from the body as a whole.

Shah et al. (1981) detected ^{14}C in the blood and liver, but not fat, of ICR mice following dermal application of [succinyl-^{14}C] malathion (1 μ Ci, 1 mg/kg). Peak blood levels were observed at 15 minutes post-application, but the level of radioactivity in the liver was highest at 60 minutes.

Distribution in humans has been determined following ingestion of a lethal amount of malathion (Morgade and Barquit, 1982). In this case, malathion was detected in the gastric contents (8621 ppm) and adipose tissue (76.4 ppm) but not in the liver. The absence of malathion in the liver may be the result of a high rate of malathion metabolism, since high levels of malathion monocarboxylic acid and malathion dicarboxylic acid were found in this tissue. High levels of malaxon (6.2 ppm) were detected in the fat.

4.3. METABOLISM

In common with other organophosphorothionate insecticides, malathion requires metabolic activation for the expression of its acute toxic effects (Casarett and Doull, 1975). This activation involves sulfur oxidation by microsomal enzymes, resulting in the production of the toxic metabolite, malaoxon. The major detoxification reactions are hydrolysis of the carboxy-ester linkages by nonspecific B type carboxyesterase dealkylation of the phosphate ester and cleavage of the P-S bond by phosphatases (March et al., 1956; Krueger and O'Brien, 1959; Bhagwat and Ramachandran, 1975). Early studies have indicated that the metabolic pathway is qualitatively similar

in insects, rodents and humans (March et al., 1956; O'Brien et al. [illegible]7; Krueger and O'Brien, 1959; Main and Braid, 1962; Fukuto and Metcalf, 1969). The pathway is illustrated in Figure 4-1.

Nomeir and Dauterman (1978) investigated the degradation of malathion by mouse liver esterases. They isolated three products: malathion monocarboxylic acid, desmethyl malathion and tetraethyl dithiodisuccinate. Malathion monocarboxylic acid was formed either with or without added glutathione; however, formation of the other products required glutathione as a cofactor. The authors speculated that desmethyl malathion may hydrolyze nonenzymatically to diethyl thiomalate, which is then oxidized to tetraethyl dithiosuccinate during isolation and purification.

Bradway and Shafik (1977) determined the urinary excretion of malathion metabolites by male Sprague-Dawley rats given malathion by gavage. Five metabolites were found. These were, in decreasing order of the amount excreted, malathion dicarboxylic acid (DCA), malathion monocarboxylic acid (MCA), dimethyl phosphorothionate (DMTP), dimethyl phosphordithioate (DMDTP) and dimethyl phosphoric acid (DMP). These same metabolites, plus monomethyl phosphate (MMP), were found in the urine of a human poisoning case; however, the relative amounts were somewhat different. The metabolites in decreasing order of concentration were MCA, DMTP, DMP, DMDTP, DCA and MMP.

Brodeur and DuBois (1967) postulated that differences in the susceptibility of immature and mature rats to malathion toxicity may be the result of differing capacities for enzymatic detoxification. They found that the livers of immature male Sprague-Dawley rats had significantly lower levels of carboxyesterase than did the livers of mature males. Administration of testosterone increased carboxyesterase activity in immature males and adult females, while castration or estradiol decreased this enzyme activity in

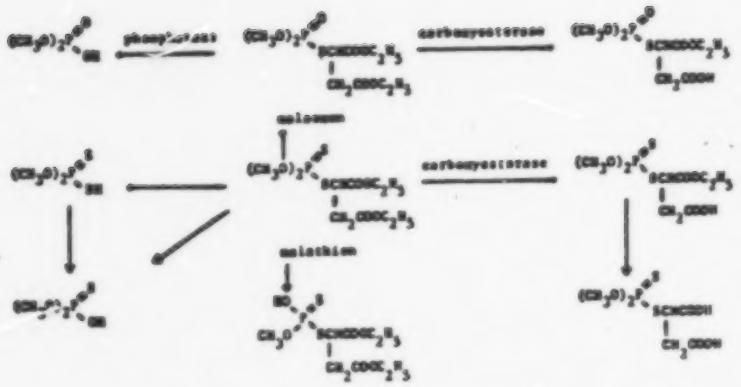


FIGURE 4-1

Metabolic Pathway of Malathion

Source: Fukuto and Metcalf, 1969

adult males. Significant levels of carboxyesterase activity were also detected in the lungs, serum and sex glands of male and female rats and in the kidneys of males. Most of this activity (88.79%) was localized in the microsomes. Miyata and Matsumura (1972) determined that rat liver 20,000 X g supernatant contains at least four distinctly different types of enzymes that degrade malathion, based on cofactor requirements and ion activation characteristics.

Talcott (1979) investigated the distribution of malathion carboxyesterases in various tissues and subcellular fractions in female Sprague-Dawley rats. The greatest malathion carboxyesterase activity, expressed as nmol hydrolyzed/minute, was found in the liver (24,000±2170), followed by serum (7490±601), kidney (4720±509), lung (370±44.8), brain (0.6) and intestinal villi (0.5). In subcellular distribution studies, most of the activity was located in the microsomes (75.5%), followed by the mitochondria (17.7%), light mitochondria (8.7%), cytosol (0.8%) and nuclei (0.7%).

Bourke et al. (1968) found that a small percentage of the malathion administered orally to rats was degraded to respiratory CO_2. Most of the administered compound was recovered in the urine as four major unidentified metabolites. One metabolite, which was not found in the urine, was isolated from the stomach contents.

Townsend and Carlson (1980, 1981) demonstrated that induction of enzymes with halogenated benzenes decreased the toxicity of malathion to male Swiss mice. The decreased toxicity correlated well with increased activity of serum and hepatic carboxylesterases.

4.4. EXCRETION

A male volunteer who had ingested 58 mg of technical grade malathion (0.84 mg/kg) excreted 22 and 23% of the dose (detected as ether-extractable

phosphates) in the urine 7.5 and 16.3 hours, respectively, after ingestion (Mattson and Sedlak, 1960). Following ingestion of a 0.16 mg/kg dose of malathion (99%), 19% of the dose was excreted in the 8-hour urine.

Rats treated intraperitoneally with ^{32}P-malathion in peanut oil at 25 or 100 mg/kg/day for 5 days excreted averages of 42 and 46%, respectively, of administered radioactivity daily in the urine (Mattson and Sedlak, 1960). Similar results were obtained following 5 daily oral doses of ^{32}P-malathion at 100 mg/kg/day: female excreted a daily average of 48%, while males excreted a daily average of 24%, of the administered radioactivity.

Bourke et al. (1968) administered 5 μ Ci (25 mg) of [succinyl-^{14}C] malathion in corn oil to six male Holtzman rats by stomach tube and measured the amount of radioactivity excreted in the urine, in the feces, and as respiratory $^{14}CO_2$. They found that 1.66% of the administered radioactivity was excreted as $^{14}CO_2$ within 8 hours and 2.77% within 24 hours. The bulk of the dose was excreted in the urine, accounting for 44.12% of the dose at 8 hours and 83.44% at 24 hours. By 24 hours, 5.51% had been excreted in the feces; however, this probably represents unabsorbed malathion, since biliary excretion does not appear to be a significant route of excretion (Ahdaya and Guthrie, 1982). Similar results have been obtained by Abd-Elraof et al. (1981) and Ahdaya et al. (1981).

Ahdaya and Guthrie (1982) administered [succinyl-^{14}C] malathion to female ICR mice by gavage. In mice in which the pyloric stomach had been ligated, <1% of the administered radioactivity was eventually found in the intestine. Most of the radioactivity (amount not given) was excreted in the urine. These data indicate that biliary excretion does not play a significant role in the excretion of malathion or its metabolites.

Shah et al. (1981) applied [succinyl-^{14}C]malathion (1 μ Ci in acetone) to the skin of female Duplin ICR mice. They estimated that 66.7% had been absorbed by 8 hours and 30.1% had been excreted by all routes (respiratory, urine, feces). They stated that excretion occurred primarily through the urine, but the relative amounts for each route were not given.

5. EFFECTS

5.1. CARCINOGENICITY

Malathion has been tested for carcinogenicity in rats in the National Cancer Institute Bioassay Program (NCI, 1978; 1979a). In the first study, groups of 50 male and 50 female Osborne-Mendel rats were fed diets containing malathion (technical) for 80 weeks (NCI, 1978). The high-dose groups were fed diets containing 12,000 ppm malathion for 3 weeks, 8000 ppm for the next 77 weeks, and a control diet for the remaining 29 weeks of the study. The low-dose groups received 8000 ppm malathion for 14 weeks, followed by 4000 ppm for 66 weeks and control diets for an additional 33 weeks. These treatments resulted in a TWA of 4700 and 8150 ppm during the 80 weeks of treatment for the low- and high-dose groups, respectively. The matched control groups contained only 15 rats/sex. Mortality was not significantly affected by malathion treatment in either sex, and there were sufficient numbers of rats at risk in each group for the detection of late-developing tumors. Body weights were lower in treated females than in control females. Higher incidences of proliferative lesions in the thyroids were observed in treated rats compared with matched controls (Table 5-1). No statistically significant dose-related trends or differences from controls (either matched or pooled) were found for C-cell or follicular cell adenomas or carcinomas in the female rats. For the male rats, a significant ($p=0.026$) positive dose-related trend for the combined incidence of follicular-cell adenomas and carcinomas was found when the incidences in pooled controls (0/46) were included in the analysis; however, no statistically significant differences were found for C-cell or follicular-cell adenomas or carcinomas between

TABLE 5-1

Incidences of Proliferative Lesions of the Thyroid in Malathion Treated Rats

	Osborne Mendel Rats[a]						F344 Rats[b]					
	Males			Females			Males			Females		
	Matched Control	Low Dose	High Dose	Matched Control	Low Dose	High Dose	Matched Control	Low Dose	High Dose	Matched Control	Low Dose	High Dose
Number of Tissues Examined	14	41	47	15	48	49	47	46	44	46	49	49
Lesion												
C-cell hyperplasia	0	1	3	0	5	3	7	1	1	7	2	1
C-cell adenoma	0	1	3	0	1	2	3	2	0	3	2	5
Follicular-cell hyperplasia	1	7	8	0	3	0	0	0	0	0	0	0
Follicular-cell adenoma	1	1	1	0	0	1	0	0	0	0	0	0
Follicular-cell carcinoma	0	2	6	0	0	3	0	0	0	0	0	0

[a]NCI, 1978

[b]NCI, 1979a

treated and control groups. Therefore, a carcinogenic effect of malathion feeding in rats was suggestive in this bioassay (NCI, 1978).

The NCI repeated the bioassay of malathion using F344 rats (NCI, 1979a). Groups of 50 rats/sex/dose received diets containing 2100 or 4000 ppm malathion (technical) for 103 weeks, followed by a control diet for an additional 2-3 weeks. Groups of 50 matched-control rats of each sex were maintained on the control diets throughout the study. Mortality was unaffected in female rats but was increased in a dose-related manner in male rats. Male rats also had dose-related decreased body weights and dose-related increased incidences of gastritis and gastric ulcers. Female rats had dose-related increased incidences of hepatic fatty metamorphosis. The incidences of thyroid lesions in the rats of this second study are included in Table 5-1. Follicular-cell tumors were absent. No significant increased incidences or dose-related trends were found for C-cell adenomas or any other type of tumor in this study. It should be noted that the high dose used in this study was less than the TWA of the low dose in the previous study.

A bioassay of malathion was also conducted in B6C3F1 mice (NCI, 1978). Groups of 50 male and 50 female mice were fed malathion in the diet at concentrations of 0, 8000 or 16,000 ppm for 80 weeks, followed by control diets for 14-15 weeks. The matched control groups contained only 10 mice/sex. Mortality was not significantly affected by malathion treatment in either sex, and there were sufficient numbers of mice at risk in each group for the detection of late-developing tumors. Body weights were lower in treated females than in control females. Increased incidences of hepatocellular carcinoma and neoplastic lesions were observed in treated male groups com-

pared with matched and pooled controls (Table 5-2). The incidences of neoplastic nodules alone or hepatocellular carcinoma alone were not statistically significantly greater in either treated group compared with either control group. There was a significant dose-related trend (p=0.016) for neoplastic nodules when the matched control was used; however, departure from linearity was significant (p=0.030). When the incidences of nodules and carcinomas were combined, the dose-related trend was significant using matched (p=0.041) or pooled controls (p=0.019). The combined incidence in the high-dose group was signficantly greater (p=0.031) than that in the pooled controls. Therefore, a carcinogenic effect of malathion feeding in mice was suggested in this bioassay (NCI, 1978).

The NCI has also conducted a bioassay using malaoxon, the metabolite of malathion responsible for its anticholinesterase activity (NCI, 1979b). F344 rats and B6C3F$_1$ mice (50/sex/species/dose) were fed diets containing 500 or 1000 ppm malaoxon for 103 weeks followed by control diet for an additional 1-2 weeks. Groups of 50 male and 50 female animals of each species were maintained as matched-controls throughout the study. No treatment-related increase in mortality was observed in any group. There were no tumors produced that could be unequivocally related to malaoxon administration and it was concluded that "under the conditions of this bioassay malaoxon was not carcinogenic for F344 rats or B6C3F$_1$ mice." There was a statistically significant incidence of C-cell carcinomas and adenomas of the thyroid in female rats, as compared with the matched controls; however, the observed incidence was within the range seen in historical control groups within this laboratory. It should be noted that the doses used in this study may not represent the maximum tolerated doses for these strains.

TABLE 5-2

Incidence of Hepatocellular Lesions in Male B6C3F1 Mice Treated with Malathion*

	Matched Control	Pooled Control	Low Dose	High Dose
Neoplastic nodule	0/10	3/49	0/48	6/49
Hepatocellular carcinoma	2/10	5/49	7/48	11/49
Neoplastic nodule or hepatocellular carcinoma	2/10	8/49	7/48	17/49

*Source: NCI, 1978

5.2. MUTAGENICITY

Bacterial mutagenicity tests of malathion have produced predominantly negative results (Table 5-3). The only positive results were obtained by Shiau et al. (1980). In mutagenicity tests using six strains of Salmonella typhimurium and two strains of Bacillus subtilis, positive results were obtained with one strain of S. typhimurium, TA1535, and 1 strain of B. subtilis, TKJ6321, in the absence of an S9 activating system. When S9 mix was added to the incubation mixture, mutagenic potency was decreased. B. subtilis TKJ6321 was much more sensitive to the mutagenic effects of malathion than was S. typhimurium TA1535. Other investigators have reported negative results with S. typhimurium TA1535, both with and without activation by mammalian S9 preparations (McCann et al., 1975; Moriya et al., 1983).

In bacterial tests for the induction of DNA-damage using 17 strains of B. subtilis, malathion has produced negative results (Shiau et al., 1980). At 300 µg/plate, malathion produced a detectable zone of inhibition but this zone was <1 mm in size and no repair-deficient mutant demonstrated measurably greater growth inhibition than its isogenic wild type. The presence or absence of S9 mix had no effect on the zone of inhibition produced by malathion. When isolated ColE1 plasmid DNA was incubated with 0.1 mg malathion/mL, however, the amount of breakage of the closed circular DNA was significantly increased, indicating that malathion has the potential to damage DNA (Griffin and Hill, 1978a,b).

In mammalian cell culture assays, malathion has been demonstrated to induce SCE (Nicholas et al., 1979; Chen et al., 1981, 1982) but has produced negative results in tests for chromosome damage (Huang, 1973). Chen et al. (1981, 1982) observed an increase in SCE frequency in Chinese hamster V79 cells at malathion concentrations of ≥20 µg/mL in the absence of

TABLE 5-3

In Vitro Mutagenicity of Malathion

Assay	Indicator Organism	Application	Concentration or Dose	Activation System (S9)	Response	Comment	Reference
Reverse mutation	S. typhimurium TA100, TA98, TA1535, TA1577	plate incorporation	NR	+/-	-	NC	McCann et al., 1975
Reverse mutation	S. typhimurium TA1535, TA1536, TA1537, TA1538, TA98, TA100	spot test plate incorporation	NR 5-300 µg/plate	+/-	-/+	Positive results were obtained at 300 µg with strain TA1535 in the absence of activation by mammalian S9 mix.	Shiau et al., 1980
Reverse mutation	S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	plate incorporation	NR	+/-	-	NC	Moriya et al., 1983
Reverse mutation	E. coli K-12/gal R^{5}18	plate incorporation	0.2 M	-	-	NC	Mohn, 1973a,b
Reverse mutation	E. coli WP2 hcr	plate incorporation	NR	+/-	-	NC	Moriya et al., 1983
Reverse mutation	B. subtilis TKJ5211, TKJ6321	spot test	NR	+/-	-/+	At 300 µg, positive results in strain TKJ6321; S9 mix reduced the mutagenic response to <2 x background.	Shiau et al., 1980
DNA-damage	B. subtilis recA1, recA8, recB2, recC5, recD3, recE4, recG13, mc-1, M45, hcr-9, fh2006-7, HJ15, T-1, 168, HA101, TKJ521, TKJ6321	spot test	NR	+/-	-	An increase in the size of the inhibition zone was observed, but was not sufficient to be classified as a clearly positive result.	Shiau et al., 1980
DNA-damage	ColE1 plasmid DNA	liquid suspension	0.1 mg/ml	-	+	NC	Griffin and Hill, 1978a,b
Chromosome damage	human hematopoietic cells, B411-4, RPMI-1788, RPMI-7191	liquid suspension	50, 100, 200 or 400 µg/ml	-	-	Cell growth was inhibited at all concentrations but no increase in chromosomal aberrations was noted.	Huang, 1973

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TABLE 5-3 (cont.)

Assay	Indicator Organism	Application	Concentration or Dose	Activation System (S9)	Response	Comment	Reference
SCE	human fetal lung fibroblasts	liquid suspension	2.4-40 µg/mℓ	-	+	For any given total dose, two exposures, 20 hours apart, were more effective than a single dose.	Nicholas et al., 1979
SCE	Chinese hamster V79	liquid suspension	10, 20, 40 or 80 µg/mℓ	+/-	+	Active at doses >10 µg/mℓ in the absence of S9 and at doses >20 µg/mℓ in the presence of S9.	Chen et al., 1981, 1982

NC = No comment

NR = Not reported

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08/23/84

mammalian S9 mix. In the presence of S9 mix, increased incidences of SCE were not observed at a concentration of 20 µg/mℓ but were seen at concentrations of 40 or 80 µg/mℓ. Nicholas et al. (1979) reported that, in human fetal lung fibroblasts, any given total dose of malathion was more effective in inducing SCEs when administered as two doses, 20 hours apart, than when administered as a single dose.

Huang (1973) grew three human hematopoietic cell lines, B411-4, RPMI-1788 and RPMI-7191 in media containing 50, 100, 200 or 400 µg malathion/mℓ for up to 50 hours. Cell growth was inhibited at all concentrations, but no increase in chromosomal aberrations was observed.

Several groups have attempted to determine the mutagenicity of malathion in vivo. Dulout et al. (1982) administered malathion (120, 240 or 480 mg/kg) to male Swiss mice by either the dermal or i.p. route. Both routes of exposure resulted in an increased frequency of micronuclei, but the frequency decreased with increasing dose. A higher frequency of micronuclei was observed following dermal application than after an i.p. dose. These contradictory results may be explained by the cell-cycle delay induced by malathion (Huang, 1973; Chen et al., 1981). Delays in the cell-cycle would prevent affected cells from maturing into the polychromatic erythrocytes that are scored in this assay.

A number of abstracts have been published, reporting the mutagenic potential of malathion in vivo; however, the experimental details are not sufficient to fully evaluate the results. Degraeve et al. (1978, 1979, 1982) administered malathion to mice (1.27-300 mg/kg) and tested for chromosome aberrations in bone-marrow-cells and spermatogonia, and for dominant lethal mutations. Negative results were reported in all of these studies.

Sylianco (1978) reported positive results in the *in vivo* micronucleus and host-mediated assays, but not in an Ames assay in the absence of S9 mix.

5.3. TERATOGENICITY

Khera et al. (1978) administered 0, 50, 100, 200 or 300 mg malathion (technical grade) in corn oil/kg to groups of 20 female Wistar rats on days 6-15 of gestation. On day 22 of gestation, the fetuses were removed, weighed and examined for viability and external malformations. The live fetuses were either cleared and stained for the detection of skeletal abnormalities or fixed in Bouin's fluid and sectioned by razor blade for the detection of internal anomalies. No evidence of a teratogenic effect of malathion was found in this study. The numbers of live fetuses/litter, dead or resorbed fetuses/litter and the fetal body weights were unaffected by treatment. Maternal body weights also were unaffected and no overt signs of toxicity were seen in the dams.

Malathion is known to produce a characteristic anomaly, parrot beak micromelia (PBM), when administered to the developing chick embryo, which results from the inhibition of two yolk-sac proteases (Wenger, 1974). This observation is of doubtful significance to mammalian systems.

5.4. OTHER REPRODUCTIVE EFFECTS

Krause et al. (1976) administered malathion to juvenile male Wistar rats (route not specified). Groups of 16 rats received 40 mg/kg on days 4 and 5 postpartum or 20 mg/kg on days 4-23 postpartum. Two rats/group were killed on days 6, 12, 18, 26, 34 and 50 postpartum and the testes were examined histologically. Slight reductions in the numbers of pachytene spermatocytes, Leydig cells, Sertoli cells and A-spermatogonia were found during the treatment period, particularly in the 40 mg/kg group. There were no treatment-related effects on body weight, testis weight or the ratio of tubules

to interstitial tissue. No effect of malathion administration could be detected by day 50. Jackson et al. (1975) fed 10-month-old Hampshire rams a diet containing 270 or 1350 ppm malathion for 11 months. No effects were observed on semen characteristics or spermatozoan morphology.

In a reproductive study, Kalow and Marton (1961) fed groups of 40 male and 40 female Wistar rats diets containing 0 or 4 g malathion (technical)/kg diet for 5 months (average dose ~240 mg/kg bw/day). No overt signs of toxicity or effects on growth were observed. After 10 weeks on these diets, 18 females and 12 males were randomly selected from the treated group and were housed in groups of 3 females and 1 male/cage for 1 week. Each male was then replaced with another male for 1 week. The same procedure was followed with controls. The number of pregnancies, number of pups and average litter size were not affected by treatment, but the number of pups alive at 7 and 21 days after birth was markedly reduced in the treated group. Of 116 pups born to control dams, 105 were alive at 7 days and 75 were alive at 21 days; of 107 pups born to treated dams, 56 were alive at 7 days and 34 were alive at 21 days. Treated pups had a higher incidence of ring tail disease than did controls at 21 days. Treated pups weighing <30 g were culled and the remaining 26 treated pups plus 26 control pups matched by weight were then continued on the experiment for 9 weeks. The treated offspring weighed less than the controls at the end of the 9 weeks ($p<0.01$).

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Three studies were located that dealt with human exposure to malathion. Perold and Bezuidenhout (1980) reported that prolonged exposure to low, but undetermined, levels of organophosphates (chiefly fenithion, but also malathion) caused symptoms in 38 employees from an agricultural college

(location not specified). Exposure resulted from the spraying of vegetable gardens, vineyards and fruit orchards surrounding the college. Symptoms included diarrhea and decreased plasma cholinesterase.

Rider et al. (1959) administered malathion (8 or 16 mg/day) and EPN (3 or 6 mg/day), both alone and in combination, orally to groups of 5-10 human subjects for up to 88 days. These investigators reported that daily doses of 16 mg malathion for 88 days produced no decrease in the red blood cell or plasma cholinesterase activity of five subjects, even though EPN was coadministered at 3 mg/day during the final 41 days. These subjects and five subjects that had received 6 mg/day of EPN for 88 days with 8 mg/day of malathion coadministered during the last 44 days were then given 16 mg/day of malathion and 6 mg/day of EPN for an additional 42 days. Slight depression of red blood cell and plasma cholinesterase activities resulted from this additional treatment, but no symptoms of toxicity were noted.

Initial studies with different groups of subjects and lower doses (8 mg/day of malathion for 32 days or 8 mg/day of malathion coadministered with 3 mg/day of EPN for 44 days) had detected no changes in plasma or red blood cell cholinesterase (Rider et al., 1959). No evidence of synergism was seen in any of these experiments.

To further define the threshold for cholinesterase inhibition by malathion in humans, Moeller and Rider (1962) administered malathion at 8 mg/day to five male subjects for 32 days, followed by the same dose of malathion plus 6 mg/day of EPN for 41 days, 3 weeks off treatment and then 16 mg/day of malathion for 47 days. An additional group of five male subjects received malathion at 24 mg/day for 56 days. Malathion was dissolved in corn oil and administered orally in gelatin capsules. Plasma and erythrocyte cholinesterase activities were compared with pretreatment values for

the same subjects. No changes in cholinesterase activity were seen at 8 mg/day or 16 mg/day of malathion. Plasma cholinesterase activity was depressed starting at 2 weeks of treatment in the group receiving 24 mg/day of malathion, with a maximum depression of 25% occurring 3 weeks after cessation of treatment. Erythrocyte cholinesterase activity was also depressed in this group; depression was observed during the last few days of treatment and during the post-treatment period. Maximum depression of erythrocyte cholinesterase activity was reached at ~3 weeks after cessation of treatment and was similar in magnitude to the depression of plasma cholinesterase. No clinical signs or symptoms of toxicity occurred at any of these dose levels, and no changes in blood counts or urinalysis values were found. Additional experiments in which EPN and malathion were coadministered gave no evidence of synergism.

Desi et al. (1976) administered malathion (Cythion, 95% malathion) at 0, 38 or 75 mg/kg bw/day to groups of 20 female CFY rats in the diet for 90 days. Effects were measured by EEG, EMG, maze-running experiments, cholinesterase determinations, blood counts, body weights, organ weights and histological examination of the liver, spleen, kidneys and lungs. Dose-related alterations indicative of increased excitability of the CNS were seen on the EEG traces and dose-related changes indicative of a prolongation of the excitatory process were seen on EMG traces. Maze-running performance was impaired slightly at both dose levels in a dose-related manner. EEG and EMG records were obtained at 90 days of treatment; maze-running was tested during the first 21 days of treatment. Both doses resulted in reduction of cerebral cortex cholinesterase activity at 21 days; these reductions were not dose-related and did not persist through 90 days. Red blood cell cholinesterase activity was reduced in the high-dose group at 21 but not at

90 days; plasma cholinesterase activity was not affected. High-dose animals had some histologic alterations in the liver (binuclear cells, basophilic clusters in the cytoplasm). No other treatment-related changes were seen.

Hazelton and Holland (1953) fed malathion (65, 90 or 99+% pure) to rats (strain not specified) for 2 years at levels of 0, 100, 1000 or 5000 ppm. Groups of 20 male rats were tested with the 65% malathion; group sizes were not specified for the tests with 90 and 99+% malathion, but both males and females were tested. In the 65% malathion study, plasma, erythrocyte and brain cholinesterase levels were normal in the 100 ppm group, moderately depressed in the 1000 ppm group and markedly depressed in the 5000 ppm group. Body weight and food consumption were depressed at 5000 ppm, mortality was lower in all treated groups than in controls and no histopathologic effects were seen in treated groups as compared with controls.

Similar results were seen in the study with 90% malathion (Hazleton and Holland, 1953) except that slight inhibition of cholinesterase activity occurred at the 100 ppm level. In the studies with the 99+% malathion (Hazelton and Holland, 1965), 500 ppm was apparently used instead of 100 ppm for the lowest dietary level and an additional dietary level of 20,000 ppm was also tested. Results were said to be similar to results with the 65 and 90% malathion, except that the females had no retardation of growth when fed 5000 ppm 99+% malathion. The 20,000 ppm level was lethal to the males and to one of three females tested. No other details were reported.

Limited information regarding the toxic effects of chronic oral administration of malathion is available from the carcinogenicity studies of the NCI (1978, 1979a). This information was presented in Section 5.1.

5.6. OTHER RELEVANT INFORMATION

The acute toxicity of malathion is summarized in Table 5-4. In addition to the direct toxicity of malathion, simultaneous exposure to other compounds can modify the toxicity of malathion. Malathion toxicity has been demonstrated to be potentiated in mice by exposure to EPN (Kobayashi, 1978) and in rats by exposure to impurities in technical grade malathion (Aldridge et al., 1979). The toxicity of malathion is unaffected by enzyme induction with phenobarbital (Menzer and Best, 1968).

Malathion has several physiological effects other than cholinesterase inhibition. Cecil et al. (1974) found that malathion treatment increases liver weight in female, but not male, rats; however, total lipids and vitamin A were not significantly different from controls. Malathion residues have been demonstrated to induce antibody production in rabbits (Centeno et al., 1970), but malathion failed to elicit delayed hypersensitivity in rats when applied epicutaneously for up to 4 weeks (Cushman, 1982). Treatment of mice with malathion (100-1500 mg/kg) inhibits the development of hypersensitivity to dinitrophenylated keyhole limpit hemocyanin (Ksiazek et al., 1982). Malathion also alters many enzymatic processes. Czajkowska and Walter (1980) found that malathion could inhibit nucleic acid synthesis in human lymphocytes. Malathion induces hyperglycemia (Ramu and Drexler, 1973) and reduces cerebral glycogen in rats (Agarwal and Matin, 1981). Gupta (1974) observed increases in blood glucose, plasma sodium, and liver, kidney, heart and spleen glycogen in rats following treatment with 500 mg malathion/kg. Malathion inhibits Na^+/K^+-ATPase *in vitro* with an I_{50} of 9.5×10^{-3} M (Riedel and Christenson, 1979), and decreases mitochondrial integrity *in vivo* (Feland and Smith, 1972; Beskid et al., 1973).

TABLE 5-4

Acute Toxicity of Malathion

Species	Route	LD_{50} (mg/kg)	Reference
Rat	oral	2800	Martin and Worthing, 1977
Rat (1-2 days old)	oral	209	Mendoza and Shields, 1977; Mendoza, 1976
Rat (6-7 days old)	oral	707	Mendoza and Shields, 1977; Mendoza, 1976
Rat (12-13 days old)	oral	1085	Mendoza and Shields, 1977; Mendoza, 1976
Rat (17-18 days old)	oral	1806	Mendoza and Shields, 1977; Mendoza, 1976
Rat	oral	340	Paul et al., 1979
Rat (male)	oral	1375	Gaines, 1960
Rat (female)	oral	1000	Gaines, 1960
Rat (male)	dermal	>4444	Gaines, 1960
Rat (female)	dermal	>4444	Gaines, 1960
Rat (female)	i.p.	741	Chauhan et al., 1973
Mouse	oral	1680	Berteau and Deen, 1978
Mouse	inhalation	>759	Berteau and Deen, 1978
Dog	oral	1344	Guiti and Sadeghi, 1969
Rabbit	dermal	4100	Martin and Worthing, 1977

Contact sensitization was induced in ~50% of the 87 male volunteers exposed dermally to a 10% solution of malathion in ethanol (Milby and Epstein, 1964). Following sensitization of five highly-sensitive individuals, very weak dilutions (1:1,000,000) of malathion produced a severe response (blistering). Approximately 3% of 200 occupationally exposed workers reacted to a 1% malathion patch test; however, none of the workers had severe enough sensitivity to leave the job.

Technical grade malathion is ~95% pure. Many of the impurities have been identified (Toia et al., 1980; Kanty et al., 1978; Umetsu, 1979). In many cases, these impurities are more toxic than malathion (Aldridge et al., 1979; Talcott et al., 1979; Imamura et al., 1983; Umezu, 1978). O,O,S-Trimethyl phosphorothioate, for example, has caused death in rats at doses as low as 15 mg/kg (Mallipudi et al., 1979; Umetsu et al., 1981). In addition, as previously mentioned, many of these impurities have been found to potentiate the toxicity of malathion (Aldridge et al., 1979). The level of impurities may increase with storage, significantly increasing the toxicity of malathion to mammals (Summer and Malik, 1982; Malik and Summer, 1982).

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

The available literature is rife with data on the acute toxicity of malathion in aquatic species. Battelle's Columbus Laboratories (1971) summarized at least 32 studies published between 1955 and 1968 on the toxic effects of malathion to fish species and 16 studies on the toxicity of aquatic invertebrates. This summary will emphasize (and be limited to) studies that determined the toxicity of malathion on several fish species for comparative purposes and on those testing fish common to the United States.

In general, early studies identified the salmonids, salmon and trout, and centrachids, sunfish and bass, as the most sensitive families of fish to malathion (U.S. EPA, 1976). More recent data, as summarized in Table 6-1, support this generalization and additionally identify the walleye (Stizostedion vitreum vitreum; Family Percidae) as relatively sensitive (Johnson and Finley, 1980). The 96-hour LC_{50} values for sensitive species fall between 0.062 and 0.285 mg/ℓ, while those of resistant species (carp, fathead minnow, catfish, goldfish and bullhead) range from 6.59-12.90 mg malathion/ℓ (Table 6-1). Pickering et al. (1962) reported the 96-hour LC_{50} for bluegills to be 0.09 mg/ℓ, while that for fathead minnows was 23.0 mg malathion/ℓ. Water temperature influenced toxicity so that LC_{50}s were lower at the preferred temperature of the fish species, 12.8°C for rainbow trout (FWS, 1965; Cope, 1965) and 23.8°C for bluegill sunfish (Macek et al., 1969).

Testing in several species of marine fish show malathion to be similarly toxic as in freshwater fish. The 96-hour LC_{50} values for bluehead (Thalassoma bifasciatum), American eel (Anguilla rostrata), Atlantic

TABLE 6-1

Acute Lethal Concentrations (LD_{50}s) of Malathion to Freshwater Fish

Species	Duration (hour)	Concentration (mg/ℓ)	Method	Reference
Brown trout, *Salmo trutta*	96	0.101	static	Johnson and Finley, 1980
Lake trout, *Salvelinus namaycush*	96	0.076	static	Johnson and Finley, 1980
Walleye, *Stizostedion vitreum vitreum*	96	0.064	static	Johnson and Finley, 1980
Coho salmon, *Oncorhynchus kisutch*	96	0.170	static	Johnson and Finley, 1980
Cutthroat trout, *Salmo clarkii*	96	0.280	static	Johnson and Finley, 1980
Rainbow trout, *Salmo gairdneri*	96	0.200	static	Johnson and Finley, 1980
Bluegill sunfish, *Lepomis macrochirus*	96	0.103	static	Macek and McAllister, 1970; Johnson and Finley, 1980
Redear sunfish, *Lepomis microlophus*	96	0.062	static	Johnson and Finley, 1980
Green sunfish, *Lepomis cyanellus*	96	0.175	static	Johnson and Finley, 1980
Largemouth bass, *Micropterus salmoides*	96	0.285	static	Macek and McAllister, 1970; Johnson and Finley, 1980

TABLE 6-1 (cont.)

Species	Duration (hour)	Concentration (mg/ℓ)	Method	Reference
Yellow perch, *Perca flavescens*	96	0.263	static	Macek and McAllister, 1970; Johnson and Finley, 1980
Carp, *cyprinas carpio*	96	6.590	static	Macek and McAllister, 1970 Johnson and Finley, 1980
Fathead minnow, *Pimephales promelas*	96	8.650	static	Macek and McAllister, 1970; Johnson and Finley, 1980
Channel catfish, *Ictalarus punctatus*	96	8.970	static	Macek and McAllister, 1970; Johnson and Finley, 1980
Goldfish, *Carassius auratus*	96	10.70	static	Macek and McAllister, 1970; Johnson and Finley, 1980
Black bullhead, *Ictalurus melas*	96	12.90	static	Macek and McAllister, 1970; Johnson and Finley, 1980
Rainbow trout, *S. gairdneri*	24	0.100	7.2°C static	FWS, 1965; Cope, 1965
Rainbow trout, *S. gairdneri*	48	0.079	7.2°C static	FWS, 1965; Cope, 1965
Rainbow trout, *S. gairdneri*	96	0.077	7.2°C static	FWS, 1965; Cope, 1965
Rainbow trout, *S. gairdneri*	24	0.085	12.8°C static	FWS, 1965; Cope, 1965
Rainbow trout, *S. gairdneri*	48	0.070	12.8°C static	FWS, 1965; Cope, 1965

TABLE 6-1 (cont.)

Species	Duration (hour)	Concentration (mg/ℓ)	Method	Reference
Rainbow trout, *S. gairdneri*	96	0.068	12.8°C static	FWS, 1965; Cope, 1965
Rainbow trout, *S. gairdneri*	24	0.130	18.3°C static	FWS, 1965; Cope, 1965
Rainbow trout, *S. gairdneri*	48	0.120	18.3°C static	FWS, 1965; Cope, 1965
Rainbow trout, *S. gairdneri*	96	0.110	18.3°C static	FWS, 1965; Cope, 1965
Redear sunfish, *L. microlephus*	96	0.170	static	Macek and McAllister, 1970
Rainbow trout, *S. gairdneri*	96	0.170	static	Macek and McAllister, 1970
Brown trout, *S. trutta*	96	0.200	static	Macek and McAllister, 1970
Coho salmon, *O. kisutch*	96	0.101	static	Macek and McAllister, 1970
Brook trout, *Salvelinus fontinalis*	96	0.130[a]	static	Post and Shroeder, 1971
	96	0.120[b]	static	Post and Shroeder, 1971
Cutthroat trout, *Salmo clarkii*	96	0.150[c]	static	Post and Shroeder, 1971
	96	0.201[d]	static	Post and Shroeder, 1971
Rainbow trout, *Salmo gairdneri*	96	0.122	static	Post and Shroeder, 1971

TABLE 6-1 (cont.)

Species	Duration (hour)	Concentration (mg/ℓ)	Method	Reference
Coho salmon, *O. kisutch*	96	0.265	static	Post and Shroeder, 1971
Striped bass, *Marone saxatilis*	96	0.039	NR	Rehwoldt et al., 1977
Banded killifish, *Fundulus diaphanus*	96	0.24	NR	Rehwoldt et al., 1977
Pumpkinseed sunfish, *Lepomis gibbosus*	96	0.48	NR	Rehwoldt et al., 1977
American eel, *Angnilla rostrata*	96	0.50	NR	Rehwoldt et al., 1977
White perch, *Raccus americanus*	96	1.10	NR	Rehwoldt et al., 1977
Guppy, *Libistes reticulatus*	96	1.20	NR	Rehwoldt et al., 1977
Carp, *Cyprinas carpio*	96	1.90	NR	Rehwoldt et al., 1977

TABLE 6-1 (cont.)

Species	Duration (hour)	Concentration (mg/ℓ)	Method	Reference
Bluegill sunfish, *Lepomis macrochirus*	24	0.220	12.7°C; static	Macek et al., 1969
	96	0.120	12.7°C; static	Macek et al., 1969
	24	0.140	18.3°C; static	Macek et al., 1969
	96	0.055	18.3°C; static	Macek et al., 1969
	24	0.110	23.8°C; static	Macek et al., 1969
	96	0.046	23.8°C; static	Macek et al., 1969
Fathead minnows, *Pimephales promelas*	96	23.0	static	Pickering et al., 1962
Bluegill sunfish, *Lepomis macrochirus*	96	0.090	static	Pickering et al., 1962
Guppies, *Lebistes reticulatus*	96	0.84	static	Pickering et al., 1962

[a]Average fish weight was 1.15 g

[b]Average fish weight was 2.13 g

[c]Average fish weight was 0.33 g

[d]Average fish weight was 1.25 g

NR = Not reported

silverside (Menidia menidia), mummichog (Fundulus heteroclitus), striped killifish (Fundulus majalis) and Northern puffer (Sphaeroides moculatus) were 0.027, 0.082, 0.125, 0.240, 0.250 and 3.25 mg malathion/ℓ, respectively (Eisler, 1970).

Data on the toxicity of malathion on aquatic crustaceans and insects are also abundant (Table 6-2). Comparatively, 96-hour LC_{50} values range from <1 µg/ℓ for several species (Gammarus fasciatus, Isoperla sp., Heptagenia sp.) to 50 mg/ℓ for juvenile crayfish, Procambarus acutus acutus. The lethal concentrations of malathion were generally lower in aquatic invertebrates than fish (compare Tables 6-1 and 6-2).

6.2. CHRONIC STUDIES

Ten-month studies with fathead minnows, Pimephales promelas, exposed to malathion at 0.58, 0.20, 0.07 and 0.03 mg/ℓ were used to determine that levels between 0.07 and 0.20 mg/ℓ would allow survival and reproduction (Mount and Stephan, 1967). Survival of adults, the apparent limiting factor, was affected at 0.58 and 0.20 mg/ℓ within 7 weeks. Reproduction and survival of embryologic stages of fish were not greatly affected at <0.20 mg/ℓ malathion. Embryo-larval stages of goldfish, Carassius auratus, had EC_{50} values of 2.61 and 3.15 mg malathion/ℓ for hatching in soft and hard water, respectively (Birge et al., 1979). The 96-hour LC_{50} for larval C. auratus was 1.20 mg/ℓ in soft water and 1.65 µg/ℓ in hard water. Spinal defects were present in 2, 6 and 25% of hatched embryos exposed at 0.6, 2.0 and 5.2 mg malathion/ℓ, respectively (Birge et al., 1979). Weis and Weis (1976) reported skeletal malformations in embryo-larval sheepshead minnows, Cyprinodon variegatus, exposed to 3.0 and 10.0 mg malathion/ℓ. Hatching was retarded in eggs exposed at 10.0 mg/ℓ and 25 and 41% of fry exposed at 3.0 and 10.0 mg/ℓ, respectively, developed bent

TABLE 6-2

Acute Lethal Effects of Malathion on Aquatic Invertebrates

Species	Duration (hour)	Concentration (mg/L)	Method	Effect	Reference
Daphnid, *Simocephalus serrulatus*	48	0.0035	static	LC_{50}	Sanders and Cope, 1966
Daphnid, *Daphnia magna*	48	0.001	static	LC_{50}	Johnson and Finley, 1980
Daphnid, *Daphnia pulex*	48	0.0018	static	LC_{50}	Sanders and Cope, 1966
Seed shrimp, *Cypridopsis vidua*	48	0.047	static	LC_{50}	Johnson and Finley, 1980
Sowbug, *Asellus brevicaudus*	96	3.0	static	LC_{50}	Johnson and Finley, 1980
Scud, *Gammarus fasciatus*	96	0.00076	static	LC_{50}	Johnson and Finley, 1980
Crayfish, *Orconectes nais*	96	0.180	static	LC_{50}	Johnson and Finley, 1980
Glass shrimp, *Palaemonetis kadiakensis*	96	0.090	static	LC_{50}	Johnson and Finley, 1980
Stonefly larvae, *Pteronarcys californica*	96	0.010	static	LC_{50}	Sanders and Cope, 1968
Stonefly larvae, *Pteronarcella bodia*	96	0.0011	static	LC_{50}	Sanders and Cope, 1968

0576p

08/23/84

TABLE 6-2 (cont.)

Species	Duration (hour)	Concentration (mg/ℓ)	Method	Effect	Reference
Stonefly larvae, *Claassenia sabulosa*	96	0.0028	static	LC_{50}	Sanders and Cope, 1968
Stonefly larvae, *Isoperla* sp.	96	0.00069	static	LC_{50}	Sanders and Cope, 1968
Damselfly, *Lestes congener*	96	0.010	static	LC_{50}	Sanders and Cope, 1968
Caddisfly, *Hydropsyche* sp.	96	0.005	static	LC_{50}	Sanders and Cope, 1968
Caddisfly, *Limnephilus* sp.	96	0.0013	static	LC_{50}	Sanders and Cope, 1968
Snipefly, *Atherix variegata*	96	0.385	static	LC_{50}	Johnson and Finley, 1980
Stonefly larvae, *Pteronarcys* sp.	96	0.01	static	LC_{50}	FWS, 1964
Stonefly larvae, *Pteronarcella* sp.	48	0.006	static	LC_{50}	FWS, 1964
Mayfly, *Heptagenis* sp.	48	0.0002	static	LC_{50}	FWS, 1964
Caddisfly, *Hydropsyche* sp.	96	0.005	static	LC_{50}	FWS, 1964
Daphnid, *Daphnia pulex*	48	0.0018	static	LC_{50}	FWPCA, 1968

0516b
08/23/84

TABLE 6-2 (cont.)

Species	Duration (hour)	Concentration (mg/ℓ)	Method	Effect	Reference
Stonefly larvae, *Pteronucella bodia*	48	6.0	static	LC_{50}	FWPCA, 1968
Scud, *Gammarus lacustris*	48	1.8	static	LC_{50}	FWPCA, 1968
Korean shrimp, *Palaemon macrodactylus*	96	0.0815	static	LC_{50}	U.S. EPA, 1976
Korean shrimp, *P. macrodactylus*	96	0.0337	flow-through	LC_{50}	U.S. EPA, 1976
Caddisfly naiad, *Hydropsyche* sp.	24	0.0129	aerated flowing	LC_{50}	Carlson, 1966
Mayfly naiad, *Hexagenia* sp.	24	0.631	aerated flowing	LC_{50}	Carlson, 1966
Juvenile crayfish, *Procambarus acutus*	96	50.0	static	LC_{50}	Carter and Graves, 1972; Cheah et al., 1980
Red crayfish, *Procambarus clarkii*	72	20.0	static	no mortality	Muncy and Oliver, 1963
Sand shrimp, *Crangon septemspinasa*	96	0.033	static; aerated	LC_{50}	Eisler, 1969
Grass shrimp, *Palaemonetes vulgaris*	96	0.082	static; aerated	LC_{50}	Eisler, 1969
Hermit crab, *Pagurus longicarpus*	96	0.083	static; aerated	LC_{50}	Eisler, 1969

05760
08/23/84

TABLE 6-2 (cont.)

Species	Duration (hour)	Concentration (mg/ℓ)	Method	Effect	Reference
Stonefly larvae, Acroneuris pacifica	96	0.0072	flow-through	LC_{50}	Gaufin et al., 1961
Stonefly larvae, Claasenia sabalosa	96	0.056	flow-through	LC_{50}	Gaufin et al., 1961
Stonefly larvae, Pteronarcys californica	96	0.10	flow-through	LC_{50}	Gaufin et al., 1961
Caddisfly larvae, Arctopsyche grandis	96	0.032	flow-through	LC_{50}	Gaufin et al., 1961; 1965
Caddisfly larvae, Hydropsyche californica	96	0.0225	flow-through	LC_{50}	Gaufin et al., 1961; 1965
Stonefly larvae, P. californica	96	0.05	static	LC_{50}	Gaufin et al., 1965
Stonefly larvae, A. pacifica	96	0.0070	static	LC_{50}	Gaufin et al., 1965

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08/23/84

spines and uncoordinated movement that prevented swimming. Exposure to malathion at 1.0 mg/ℓ had no observed effect on egg hatching or fry development and survival (Weis and Weis, 1976).

Circulatory anomalies were reported in medaka, Oryzias latipes, exposed to malathion at 10.0, 20.0, and 40.0 mg/ℓ from early blastula stage to hatching or death (Solomon and Weis, 1979). Abnormalities included undifferentiated hearts, edema, clotting, bidirectional ventricle blood flow and irregular heart beat. No abnormalities in development were reported in embryos exposed at 5.0 mg malathion/ℓ (Solomon and Weis, 1979).

Based on 60-day embryo-larval tests, the MATC for malathion in carp, Cyprinus carpio, was reported to be between 0.045 and 0.055 mg/ℓ (Verma et al., 1981).

Studies were conducted with cutthroat trout, Salmo clarkii, exposed to malathion at 0.6 and 1.0 mg/ℓ or at 4 and 8 mg/kg diet for 30 days to determine the effect on brain acetylcholinesterase activity (FWS, 1964, 1965). A decrease in brain acetylcholinesterase activity was reported in fish exposed at 1.0 mg/ℓ and 8.0 mg/kg diet. The fish bathed at 1 mg/ℓ, however, had lower brain acetylcholinesterase activity than those treated by dietary malathion at 8.0 mg/kg. After 10 months of exposure, brain acetylcholinesterase levels were decreased up to 35% in six species of fish exposed to malathion at 0.01 mg/ℓ (Rehwoldt et al., 1977).

Studies conducted with eggs, embryos and metamorphosing stages of the bullfrog, Rana tigerina, indicated that malathion affects development of this species at levels as low as 0.10 mg/ℓ (Mohanty-Hejmadi and Dutta, 1981). No tadpoles, exposed from eggs to 0.01 mg/ℓ, survived past 56 days or metamorphosed, while control tadpoles metamorphosed by 33 days. Feeding stage tadpoles exposed at 0.10 mg malathion/ℓ survived only until 60 days

and none metamorphosed. Tadpoles treated from the limb-bud stage onward at 2.0 mg malathion/ℓ metamorphosed as did controls, but yielded smaller frogs (Mohanty-Hejmadi and Dutta, 1981).

Injection of 3 µℓ of malathion into the yolk sac of prelimb-bud stage embryos of the snapping turtle, Chelydra serpentina, resulted in up to 99% malformations among developing embryos (Mitchell and Yntema, 1973). Axial and appendicular skeletal malformations and delayed or arrested development were reported. Malathion exposure to the exterior of the eggs at 1, 5 or 10 µℓ/egg also produced malformations in embryos, indicating penetration of the toxicant (Mitchell and Yntema, 1973).

6.3. PLANT EFFECTS

Malathion at 100 mg/ℓ was inhibitory on the growth of Chlorella pyrenoidosa but lower levels had little effect (Christie, 1969). After 7 days of exposure, malathion at 100 mg/ℓ also reduced the growth of mixed algae isolated from a waste stabalization pond (containing Scenedesmus sp., Chlorella sp., Englena sp. and Schroderia sp.) (Christie, 1969). Growth rate of Amphiprora sp. was significantly ($P<0.05$) supressed during 48 hours of exposure to 10 mg malathion/ℓ (Maly and Ruber, 1983). Four other species of algae, Amphora coeffeaformis, Nitzschia closterium, Chlorococcum sp. and Gonyaulax sp., were not affected at 10 mg/ℓ.

6.4. RESIDUES

Malathion has been detected in samples of water from Lake Erie at levels as high as 0.0018 mg/ℓ, although most samples (145/149) contained undetectable levels (Konasewich et al., 1978). Because malathion degrades rather rapidly, its occurrence is sporadic and it would not be expected to persist (U.S. EPA, 1976; Mulla et al., 1981).

6.5. OTHER RELEVANT INFORMATION

Additional information pertinent to the aquatic toxicity of malathion could not be located in the available literature.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The ACGIH (1980, 1982) has established a TLV of 10 mg/m³. According to the Code of Federal Regulations, the U.S. EPA has established residue tolerances for raw agricultural commodities and for food ranging from 0.1-12 ppm (40 CFR 180.11; 21 CFR 193.260). The (WHO/FAO) has recommended an ADI of 0.02 mg/kg bw for malathion (Vettorazzi, 1975) based on a NOEL of 0.2 mg/kg bw/day (32-88 days) for plasma and red blood cell cholinesterase inhibition in humans (Moeller and Rider, 1962; Rider et al., 1959) and a safety factor of 10.

7.2. AQUATIC

A freshwater and marine criterion for malathion was established at 0.0001 mg/ℓ (U.S. EPA, 1976).

8. RISK ASSESSMENT

Three NCI bioassays have failed to conclusively demonstrate a carcinogenic effect of malathion (NCI, 1978, 1979a) or its principal active metabolite, malaoxon (NCI, 1979b). IARC (1983) reviewed these data and concluded that the data do not constitute evidence that malathion or malaoxon are carcinogenic to experimental animals or that malathion would be carcinogenic to humans.

Malathion has consistently given negative results in bacterial mutagenicity assays but has increased the frequency of SCE in mammalian cell culture assays (see Section 5.2.).

Malathion was not teratogenic or fetotoxic when administered orally at 50-300 mg/kg bw/day to pregnant rats on days 6-15 of gestation (Khera et al., 1978). Adverse effects on spermatogenesis resulted from the administration of malathion (by an unspecified route) to male rats at 20 mg/kg bw/day on days 4-23 of life or 40 mg/kg bw/day on days 4 and 5 of life (Krause et al., 1976). Although reproduction was not affected, survival of the offspring through weaning was markedly reduced when male and female rats were fed 240 mg/kg bw/day of malathion (Kalow and Marton, 1961).

Two studies of cholinesterase inhibition in humans were designed primarily to detect possible synergism between malathion and EPN, and also to give limited information regarding the threshold for inhibition of plasma and red blood cell cholinesterase by malathion. Oral administration of 8 mg malathion/day for 32 days or of 16 mg malathion/day for 47 days followed by coadministration of the same dose with 3 mg EPN/day for an additional 41 days produced no inhibition of plasma or red blood cell cholinesterase (Rider et al., 1959; Moeller and Rider, 1962). Oral administration of 24 mg malathion/day for 56 days, however, produced depressions in both plasma and

red blood cell cholinesterase activities; maximum depression of ~25% in both activities occurred ~3 weeks after cessation of treatment (Moeller and Rider, 1962). Thus, 16 mg malathion/day may be a NOEL for humans. It is unclear whether 24 mg malathion/day would be a NOAEL or a LOAEL because the depression of cholinesterase activity became more pronounced during the post-treatment period, raising the possibility that marked effects might have occurred had the duration of treatment been longer. Assuming a body weight of 70 kg for the male subjects used in these studies, 16 and 24 mg malathion/day would correspond to 0.23 and 0.34 mg/kg bw/day.

Plasma, red blood cell and brain cholinesterase inhibition and potential histopathological effects were investigated in a 2-year feeding study in the rat (Hazleton and Holland, 1953). In studies with malathion of 90% purity, 100 ppm in the diet produced "a very slight inhibition of cholinesterase," while 1000 ppm produced moderate and 5000 ppm produced marked depression in plasma, red blood cell and brain cholinesterase activities. Malathion of 99+% purity produced similar results, although the lowest dose tested may have been 500 rather than 100 ppm. No treatment-related histopathologic changes were observed in this study.

The initial NCI carcinogenicity study (NCI, 1978) of malathion provided little information on systemic toxicity. An additional study of technical malathion at dietary levels of 2100 and 4000 ppm in F344 rats (NCI, 1979a) reported dose-related increases in mortality among the males. Histopathologic effects included dose-related increased incidences of gastritis and gastric ulcers in the males and dose-related increased incidences of hepatic fatty metamorphosis in the females.

The available chronic feeding studies appear to define NOAELs for the rat at 100-1000 ppm malathion in the diet (Hazleton and Holland, 1953), with

adverse effects becoming apparent at 2100 ppm (NCI, 1979a). Assuming that a rat consumes the equivalent of 5% of its body weight daily in food, 100, 1000 and 2100 ppm correspond to 5, 50 and 105 mg/kg bw/day.

Some adverse effects have been noted in subchronic experiments at dosages of 20-75 mg/kg bw/day of malathion. These include impairment of the maze-running performance of rats treated orally with 38 or 75 mg/kg bw/day of malathion (Desi et al., 1976) and reversible impairment of spermatogenesis in male rats treated (by an unspecified route) with 20 mg/kg bw/day (Krause et al., 1976). Therefore, the NOAEL of 5 mg/kg bw/day from the chronic feeding study in the rat is a more appropriate basis for an ADI than is the NOAEL of 50 mg/kg bw/day. Applying an uncertainty factor of 100 to extrapolate from animal data and to account for differences in human sensitivity results in an ADI of 0.05 mg/kg bw/day, or 3.5 mg/day for a 70 kg man. This value is slightly higher than the ADI that can be estimated from the NOEL of 16 mg/day (0.23 mg/kg bw/day) for plasma and red blood cell cholinesterase inhibition in humans (Rider et al., 1959; Moeller and Rider, 1962), using the approach of the WHO/FAO (see Section 7.1.). Applying an uncertainty factor of 10 to account for differences in human sensitivity results in an ADI of 0.023 mg/kg bw/day, or 1.6 mg/day for a 70 kg man. In view of the uncertainty regarding the threshold dose for adverse effects in humans, the more conservative ADI based on the human studies is preferable.

Statements concerning available literature in this document refer to published, quotable sources and are in no way meant to imply that confidential data, which this document could not address, are not in existence. These data, which are considered Confidential Business Information (CBI), are available in summary form as a CBI Appendix that can be accessed by individuals with appropriate clearance. Conclusions from the CBI Appendix regarding risk assessment can, however, be presented in this chapter.

The CBI Appendix to this document reviews other animal data, but no change in the above risk assessment is warranted. The above ADI based on the human studies is virtually identical to the ADI of 0.02 mg/kg bw/day reported by the Office of Pesticide Programs of the U.S. EPA and reviewed in the risk assessment section of the CBI Appendix. Both ADIs appear to be based upon the same human studies.

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE

Most of these searches were conducted in February, 1983; a few were conducted March-May, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 7 and 8th), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. TLVs: Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981). Cincinnati, OH. 486 p.

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In addition, during the revision of this profile, the July 1981 Final Draft of the Malathion Multimedia Document (prepared by Biospherics Inc. for the Environmental Criteria and Assessment Office of the U.S. EPA, Cincinnati, OH) was reviewed to ensure that no key studies had been overlooked.